HARBOR: A Phase 2/3 Study of BLU-263 in Patients With Indolent Systemic Mastocytosis and Monoclonal Mast Cell Activation Syndrome

M. Castells, V. Bhavsar, K. He, R. Scherber, C. Akin

**Introduction**

- Systemic mastocytosis (SM) is a myeloid neoplasm driven by the KIT D816V mutation in ~95% of cases.
- The KIT D816V mutation leads to increased accumulation of aberrant mast cells (MCs) in bone marrow, skin, gastrointestinal tract, and other organs, which can result in chronic and debilitating symptoms that negatively impact quality of life.
- Most patients with SM have non-advanced forms, including the World Health Organization (WHO)-classified variant of indolent SM (ISM).
- MC infiltration in the skin is uncommon in ISM but is always present.
- Approximately 5% of patients with ISM progress to advanced forms of SM associated with poor survival.
- Monoclonal mast cell activation syndrome (mMCAS) is a rare MC disease which does not meet the WHO diagnostic criteria for SM but is defined by the presence of the KIT D816V mutation.
- Despite conventional therapy, there remains an unmet need for ISM and mMCAS.
- BLU-263 is a novel, oral, next-generation investigational tyrosine kinase inhibitor (TKI) with high selectivity and potency for KIT D816V, and minimal central nervous system penetration.
- Preclinical data has demonstrated the high potency of BLU-263 for KIT D816V in both biochemical (Kd=0.24 nM) and cellular (IC50 = 0.4 nM) assays.
- Phase 1 findings demonstrated the safety of BLU-263 across all tested doses in healthy participants, and the corresponding pharmacokinetics were linear across the dose ranges in single ascending and multiple ascending dose cohorts, with the half-life supporting once-daily (QD) dosing.

**BLU-263 kinome**

- **Part 1** (N = 100)
  - **RD determination**
    - **Part M** (mMCAS/Exploratory): Open-label Part M (mMCAS/Exploratory) studies: BLU-263 QD at 25 mg, 50 mg, or 100 mg QD
    - BLU-263 dose is titrated to an RD.

- **Part 2** (N ≈ 303)
  - **Primary endpoint:** Median change in ISM-SAF TS and ISM-SAF TS
  - **Secondary endpoints:**
    - Median change in ISM-SAF Symptom Score
    - Mean change in ISM-SAF TS
    - Mean change in ISM-SAF Individual Symptom Score
    - Median change in ISM-SAF TS

**Key eligibility criteria**

- **Inclusion criteria**
  - Age ≥ 18 years old (≥ 16 years old if permitted by local regulations)
  - ECOG performance status is 0–2
  - Moderate-to-severe symptoms based on the ISM-SAF mean total symptom score (Part 1)
  - Pathologically and centrally confirmed diagnosis of ISM by BM biopsy and central review of B- and C-findings according to WHO diagnostic criteria
  - Part 1, Part 2 groups
  - ISM-SAF/TS by an independent adjudication committee
  - Prior treatment with any targeted KIT inhibitors
  - Received the following therapy prior to first dose of study drug:
    - Radiotherapy or psoralen and ultraviolet A therapy (≤14 days before beginning the screening assessments)
    - Any hematopoietic growth factor (≤14 days before beginning the screening assessments)
  - Patient is currently receiving an investigational agent in another interventional study

- **Exclusion criteria**
  - Failed to achieve adequate symptom control for ≥1 baseline symptoms (Part 1, Part 2, PK groups)
  - Patients must have symptoms consistent with mast cell activation (despite BSC) in ≥2 organ systems (SM M)

**Study objectives and design**

- The phase 2/3 HARBOR trial (NCT04910885) is a randomized, double-blind, placebo-controlled study designed to determine the recommended dose (RD) of BLU-263 and to evaluate the safety, tolerability, and efficacy of BLU-263 in patients with ISM or mMCAS whom have not previously received any targeted KIT inhibitor therapy and in whom symptoms are not adequately controlled by best supportive care (BSC).
- Objective measures of BLU-263 efficacy include changes from baseline in bone marrow MC burden, serum tryptase, and peripheral blood KIT D816V variant allele frequency.
- All patients will also be receiving BSC.
- In Part 1, patients may receive placebo or BLU-263 at 25 mg, 50 mg, or 100 mg QD. Once an RD is determined from Part 1, patients will roll over to Part 3 to evaluate open-label, long-term safety and efficacy of BLU-263.
- In Part 2, patients receiving BLU-263 or placebo at the recommended Part 2 dose for 24 weeks to evaluate the proportion of patients achieving a meaningful reduction in symptom scores. Patients in Part 2 will also roll over to the open-label Part 3 extension.
- Two pharmacokinetic (PK) groups receiving BLU-263 in an open-label fashion, prior to or concurrent with Part 1 and Part 2, are planned to better characterize the PK and safety of BLU-263 in patients with ISM with varying symptom burden.

**Key study endpoints**

**Primary endpoints**

- **Part M** (mMCAS)
  - Proportion of patients achieving ≥30% reduction in MC-Gol
  - ≥50% reduction and mean change in measures of MC burden

**Secondary endpoints**

- **Part M** (mMCAS)
  - Mean change in ISM-SAF Individual Symptom Scores
  - Mean change in ISM-SAF TS
  - Mean change in ISM-SAF Individual Symptom Score
  - Mean change in ISM-SAF TS
  - Mean change in ISM-SAF Individual Symptom Score

**Exploratory endpoints**

- **Part M (mMCAS)
  - Proportion of patients achieving ≥30% reduction in MC-Gol
  - ≥50% reduction and mean change in measures of MC burden

**HARBOR study design**

- **Part M** (mMCAS/Exploratory) studies: BLU-263 QD at 25 mg, 50 mg, or 100 mg QD

**Enrollment and current status**

- Recruitment has started and enrollment is planned globally at approximately 70 sites in 15 countries worldwide.
- Current study sites:
  - Recruitment has started and enrollment is planned globally at approximately 70 sites in 15 countries worldwide.
  - For more information visit:

**Summary**

- The phase 2/3 HARBOR study is designed to seamlessly assess the safety, efficacy, and tolerability of BLU-263 as a potential treatment option to reduce symptom burden for patients with ISM and mMCAS and is currently recruiting for Part 1 and PK Groups.

**References**


**Disclosures**

- The research was funded by Blueprint Medicines Corporation. The authors had full editorial control of the poster and provided their final approval of all content. MC is a consultant for and a PI on clinical trials with Blueprint Medicines Corporation, receives author fees from UpToDate, and is a member of the editorial board for Annals of Allergy, Asthma & Immunology. VB, KH, and RS are current employees and shareholders of Blueprint Medicines Corporation. CA has received consulting fees and research support from Blueprint Medicines Corporation and consulting fees from Novartis.